

## Treatment of Combined Hyperlipidemia: Whether and How

Based on a presentation by Robert H. Knopp, MD

### *Presentation Summary*

Combined hyperlipidemia is defined as a condition characterized by elevated triglyceride levels (>200 mg/dL), borderline to elevated LDL-cholesterol levels, and low HDL-cholesterol levels. Combined hyperlipidemia is commonly associated with the insulin-resistance syndrome, which includes abdominal obesity, hypertension, and diabetes. Recent evidence suggests that elevated plasma triglyceride levels are a risk factor for cardiovascular disease that are independent of HDL-cholesterol levels, and it is agreed that

hypertriglyceridemia is a marker for other cardiovascular risk factors. Hypertriglyceridemia, in the presence of an LDL/HDL cholesterol ratio greater than 5, confers greater risk in several studies. Using a low-saturated-fat diet, a statin, and/or niacin are helpful to patients with combined hyperlipidemia. A statin combined with a fibrate is not usually advised. Niacin can be a successful treatment for most patients if used at moderate doses, if aspirin is taken first, during the first week of treatment, and if ingested with food, and no hot liquids.

In 1993 the NCEP<sup>1</sup> defined combined hyperlipidemia as elevated LDL-C levels plus elevated or borderline triglyceride levels (Table 1). Robert H. Knopp, MD, Professor of Medicine at the University of Washington School of Medicine in Seattle ex-

plained the pathophysiology of combined hyperlipidemia.

"In combined hyperlipidemia," Dr. Knopp told listeners, "both the LDL cholesterol and triglyceride levels are significantly elevated values, although 200 mg/dL for triglycerides does not often cause worry in the clinical setting."

**Table 1.** Combined Hyperlipidemia

Elevated Triglycerides:	>200 mg/dL (borderline) >400 mg/dL (elevated)
Elevated LDL cholesterol:	>130 mg/dL (borderline) >160 mg/dL (high risk) >190 mg/dL (very high risk)

### **Pathophysiology of Combined Hyperlipidemia**

Unlike classical familial hypercholesterolemia, combined hyperlipidemia does not have a single genetic etiology. Its most common manifestation is insulin resistance syndrome, or syndrome X. This condition has insulin resistance as its fundamental etiology. Abdominal obesity, hypertension, and diabetes in syndrome X are consistently associated

with an elevated triglyceride level, a low HDL-C level, and variable elevations of LDL-C.

Combined hyperlipidemia is characterized by a genetic overproduction of apolipoprotein-B-containing lipoproteins, including very-low-LDL, intermediate density lipoprotein (which falls between the LDL and HDL), and LDL which is also known as the remnant lipoprotein. All of the individuals who have insulin resistance, obesity, and diabetes also have overproduction of apolipoprotein B and the lipoprotein features of combined hyperlipidemia. Small dense LDL-C particles are another feature of combined or familial combined hyperlipidemia.

#### Is Triglyceride a Risk Factor?

Whether an elevated triglyceride level is a risk factor is probably one of the most controversial issues in lipidology, said Dr. Knopp. For a long time triglycerides were regarded as the inverse of HDL, and HDL was viewed as the risk factor. However, a recent meta-analysis of 17 studies indicated that triglycerides are an independent risk factor for cardiovascular disease, especially in women.<sup>2</sup> In patients with diabetes, elevated triglycerides may be a stronger risk factor for heart disease than elevated cholesterol, he added.

"Postprandial triglyceride elevations appear to be an additional independent predictor of cardiovascular risk, even beyond fasting triglyceride levels," Dr. Knopp said.

Recent evidence suggests that intermediate density lipoproteins carry an abundance of triglycerides, and triglycerides may be an even stronger risk factor for cardiovascular disease and carotid artery disease than LDL-C itself.

In addition to evidence that triglycerides are an independent risk factor, hypertriglyceridemia is a marker for a number of other serious risk factors: decreased plasma HDL-C, small dense LDL-C, increased glucose, increased insulin, increased systolic and diastolic

blood pressure, and elevated serum clotting factors. All these risk factors are improved by lowering triglyceride levels and by weight loss, Dr. Knopp explained.

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Several prospective studies show that the degree of risk for elevated triglyceride level depends on whether the LDL/HDL ratio is elevated. A ratio greater than 5 refers to an LDL-C level that is 5 times higher than the HDL-C level. In this instance, elevated triglyceride confers increased risk for cardiovascular disease.<sup>3</sup>

The Helsinki Heart Study prospectively established the value of lowering triglycerides in those individuals with an elevated LDL/HDL ratio of 5.<sup>4</sup> Those who had triglycerides >200 mg/dL and were untreated had an increased risk of coronary heart disease, while patients treated with gemfibrozil had a marked reduction in risk.

#### Dietary and Drug Precautions

Use of the equivalent of the American Heart Association's Step I and II diets in combined hyperlipidemics produces a significant reduction in insulin level and blood pressure. Diet can be beneficial with respect to treating associated risk factors in combined hyperlipidemia, as well as LDL-C and apolipoprotein B. Reductions in apolipoprotein B with dietary intervention alone are on the order of 13% [RH Knopp, unpublished data, September, 1996].

The HMG-CoA reductase inhibitors are probably the first choice for treatment of combined hyperlipidemia, because of their great efficacy, Dr. Knopp said. These drugs produce not only a dose-related reduction in LDL-C, but

also a modest increase in HDL-C levels. One can amplify the statin effects on LDL-C and HDL-C with a bile acid resin, but the triglyceride level goes up when the resin is added. It is undesirable, therefore, to combine a statin and resin, according to Dr. Knopp. He added that low doses of niacin can be combined with a statin to produce more desirable effects, but currently available time-release forms of niacin are generally less effective.

"It may be a good idea to try to use plain niacin first," he told listeners. "The most important thing to remember is that fibrates alone don't lower LDL-C in the presence of hypertriglyceridemia. Our preference for management of combined hyperlipidemia is the combination of niacin and a statin."

It should be kept in mind that myositis can occur with the combination of fibrates and a statin. However, one meta-analysis of 394 patients in 17 different prospective studies suggested that the risk of myositis was not as high as previously claimed.<sup>5</sup>

Dr. Knopp advised that niacin should be used sensibly. Aspirin should be given before each dose during the first week of treatment. Hot liquids should not be consumed within 30 to 60 minutes of taking niacin. Niacin should be taken at the end of a meal.

### Primary Vs. Secondary Prevention in Combined Hyperlipidemia

Treat to the NCEP's LDL-C goals, advised Dr. Knopp, which would be <130 mg/dL or 160 mg/dL for primary prevention based on risk factors. A reductase inhibitor is an excellent choice because of ease and efficacy of cholesterol lowering, but he added that niacin is also a good choice because it treats triglyceride elevation, high LDL-C levels, and low HDL-C levels.

In secondary prevention of combined hyperlipidemia, the target goal LDL-C level is <200 mg/dL. Dr. Knopp recommended initiating treatment with a re-

ductase inhibitor and adding niacin if the triglyceride level is >100 mg/dL. In both settings, a reasonable goal is to lower the triglyceride to <200 mg/dL and raise the HDL-C as much as possible.

### Conclusion

Hypertriglyceridemia is an independent risk factor for coronary heart disease in patients with combined hyperlipidemia. Hypertriglyceridemia is also a marker for additional risk factors. Dietary intervention with associated weight loss will help improve several metabolic risk factors, and drug treatment with a reductase inhibitor and/or niacin is a rational approach, specifically to manage the abnormal levels of triglyceride, LDL-C, and HDL-C.

### ... REFERENCES ...

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